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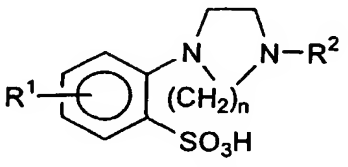
(54) Title: MEDICAMENT INHIBITING SODIUM/CALCIUM EXCHANGE SYSTEM



(I)

(57) Abstract: A medicament for inhibiting sodium/calcium exchange system which comprises as an active ingredient a substance selected from the group consisting of an aminobenzenesulfonic acid derivative represented by the following general formula (I) and a salt thereof, and a hydrate thereof and a solvate thereof: wherein R^1 represents a hydrogen atom, a C_1-C_6 alkyl group and the like; R^2 represents a hydrogen atom, a C_1-C_6 alkyl group, or a C_7-C_{12} aralkyl group; and n represents an integer of from 1 to 4. The medicament is useful for suppression of intracellular calcium accumulation generated under very severe dyscrasic condition as a result of clinically-occurred combination of ischemia/reperfusion and intracellular sodium increase.

DESCRIPTION

MEDICAMENT INHIBITING SODIUM/CALCIUM EXCHANGE SYSTEM

Technical Field

The present invention relates to a medicament which inhibits sodium/calcium exchange system.

Background Art

In ischemic heart disease such as myocardial infarction and angina pectoris, coronary blood flow blocking for a certain period of time and resumption of coronary blood flow by the recanalization therapy will occur. It is known that, following the recanalization, a rapid calcium ion inflow arises intracellularly from outside of myocardium cells, and subsequently, through various calcium dependent reactions such as activation of a calcium dependent protease, activation of a calcium dependent lipid decomposition enzyme, and reduction of energy generation, irreversible cardiomyopathy is caused. It is considered that the calcium inflow is based on sodium flow into the cells, which conjugates with extracellular excretion of protons accumulated in the cells during the ischemia and occurs through sodium/proton exchange system, and is also based on calcium flow into the cells, which conjugates with extracellular excretion of sodium in the cells and occurs through sodium/calcium exchange system.

As far as the inventors of the present invention are aware, no agent is known at present which suppresses intracellular calcium accumulation that is generated under very severe dyscrasic conditions as a result of combination of the clinically-occurred ischemia/reperfusion and the increase of intracellular sodium.

Aminobenzenesulfonic acid derivatives which have suppressing action on

hyper intracellular accumulation of calcium ion in myocardium cells or vessel smooth muscles are known (Japanese Patent Unexamined Publication (KOKAI) No. 3-7263). As for these compounds, it is known that the compounds are potentially useful as preventive and therapeutic medicaments for ischemic heart disease, heart failure, hypertension, arrhythmia and the like based on suppression or reduction of cardiomyopathy, dysfunction of heart conduction and the like, without β receptor stimulant-like action, β receptor blocker-like action, or calcium channel antagonist-like action (Japanese Patent Unexamined Publication (KOKAI) No. 3-7263 and Japanese Patent Unexamined Publication (KOKAI) No. 4-139127). Japanese Patent Unexamined Publication (KOKAI) No. 10-298077 discloses that the aforementioned compounds have remarkable improving effect on heart hypofunction under pathological cardiomyopathy, and also have improving effect on long-term survival rate of idiopathic cardiomyopathy to achieve prolongation of life of a patient. In addition, International Publication WO 99/40919 discloses that the aforementioned compounds have promoting effect on calcium ion uptake by myocardium sarcoplasmic reticulum, and are useful for therapeutic treatment or prevention of dysfunction of dilatation of heart.

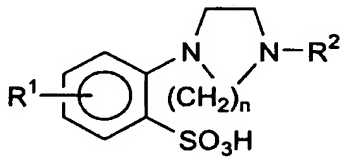
However, these publications fail to disclose whether the aforementioned compounds suppress intracellular calcium accumulation that is generated under very severe dyscrasic conditions as a result of clinically-occurred combination of the ischemia/reperfusion and the intracellular sodium increase. It is already known that the aforementioned compounds suppress the increase of myocardium calcium content resulting from ischemia/reperfusion (calcium overload). However, it has not yet been known to date whether or not the aforementioned compounds suppress calcium increase even under severe dyscrasic conditions such as mentioned above.

Disclosure of the Invention

An object of the present invention is provide a medicament which suppresses intracellular calcium accumulation that is generated under a severe dyscrasic condition as a result of clinically-occurred combination of ischemia/reperfusion and intracellular sodium increase.

The inventors of the present invention conducted various studies to achieve the foregoing object. As a result, they found that specific aminobenzenesulfonic acid derivatives or salts thereof, or hydrates thereof or solvates thereof had inhibitory action against sodium/calcium exchange system, and based on said action, the substances suppressed intracellular calcium accumulation generated under severe dyscrasic conditions as a result of clinically-occurred combination of ischemia/reperfusion and intracellular sodium increase.

The present invention thus provides a medicament for inhibiting sodium/calcium exchange system which comprises as an active ingredient a substance selected from the group consisting of an aminobenzenesulfonic acid derivative represented by the following general formula (I) and a salt thereof, and a hydrate thereof and a solvate thereof:



... (I)

wherein R^1 represents a hydrogen atom, a C_1-C_6 alkyl group, a C_3-C_7 cycloalkyl group, a halogenated C_1-C_4 alkyl group, a halogen atom, or a C_6-C_{12} aryl group; R^2 represents a hydrogen atom, a C_1-C_6 alkyl group, or a C_7-C_{12} aralkyl group which may have one or more substituents selected from the group consisting of cyano group, nitro group, a C_1-C_6 alkoxyl group, a halogen atom, a C_1-C_6 alkyl group, and amino group; and n represents an integer of from 1 to 4.

As a preferred embodiment of the present invention, provided are the aforementioned medicament for therapeutic and/or preventive treatment of dysfunction resulting from ischemia/reperfusion; the aforementioned medicament for suppressing increase in myocardium calcium content induced by dysfunction resulting from ischemia/reperfusion; and the aforementioned medicament for suppressing increase of myocardium calcium content which is generated under condition of a combination of ischemia/reperfusion and increase of myocardium sodium content.

From another aspect, provided is an inhibitor against sodium/calcium exchange system which comprises a substance selected from the group consisting of an aminobenzenesulfonic acid derivative represented by the above general formula (I) and a salt thereof, and a hydrate thereof and a solvate thereof.

From further aspect, provided is a use of a substance selected from the group consisting of an aminobenzenesulfonic acid derivative represented by the above general formula (I) and a salt thereof, and a hydrate thereof and a solvate thereof for manufacture of the aforementioned medicament.

From still further aspect, provided are:

a method for inhibition of sodium/calcium exchange system which comprises the step of administering to a mammal including human an effective amount of a substance selected from the group consisting of an aminobenzenesulfonic acid derivative represented by the above general formula (I) and a salt thereof, and a hydrate thereof and a solvate thereof:

a method for therapeutic and/or preventive treatment of a dysfunction resulting from ischemia/reperfusion, which comprises the step of administering to a mammal including human a therapeutically and/or preventively effective amount of a substance selected from the group consisting of an aminobenzenesulfonic acid derivative represented by the above general formula (I) and a salt thereof, and a hydrate thereof and a solvate thereof:

a method for suppressing increase of myocardium calcium content induced by a dysfunction resulting from ischemia/reperfusion, which comprises the step of administering to a mammal including human an effective amount of a substance selected from the group consisting of an aminobenzenesulfonic acid derivative represented by the above general formula (I) and a salt thereof, and a hydrate thereof and a solvate thereof: and

a method for suppressing increase of myocardium calcium content which is generated under condition of a combination of ischemia/reperfusion and increase of myocardium sodium content, which comprises the step of administering to a mammal including human an effective amount of a substance selected from the group consisting of an aminobenzenesulfonic acid derivative represented by the above general formula (I) and a salt thereof, and a hydrate thereof and a solvate thereof.

Best Mode for Carrying out the Invention

The medicament of the present invention comprises a substance selected from the group consisting of an aminobenzenesulfonic acid derivative represented by the above general formula (I) and a salt thereof, and a hydrate thereof and a solvate thereof as an active ingredient, and has inhibitory action against sodium/calcium exchange system. As demonstrated by the example given below, the medicament of the present invention is effective for suppressing increase of intracellular calcium content which is generated under very severe dyscrasic conditions as a result of combination of clinically-occurred ischemia/reperfusion and increase of intracellular sodium.

A degree of myocardiopathy resulting from ischemia/reperfusion correlates a period of ischemia. Larger amounts of protons become accumulated in myocardial cells as a metabolic product when ischemia period is prolonged, and a large amount of sodium flows into the myocardial cells as exchange for the protons through

sodium/proton exchange system. Subsequently, in exchange for the sodium which is increased intracellularly, a still larger amount of calcium flows into the myocardial cells through sodium/calcium exchange system. Based on the suppressing action against the sodium/calcium exchange system, the medicament of the present invention can suppress the intracellular calcium accumulation generated under the very severe dyscrasic conditions as a result of the combination of the ischemia/reperfusion and the increase of intracellular sodium. Accordingly, even when an ischemia period is prolonged by some reasons such as a delay in patient conveyance to a hospital after an ischemic heart stroke and an unsuccessful treatment of recanalization, the medicament of the present invention can effectively suppress myocardiopathy.

Active ingredients of the medicament of the present invention includes substances selected from the group consisting of aminobenzenesulfonic acid derivatives represented by the following general formula (I) and salts thereof, and hydrates thereof and solvates thereof.

In the aforementioned general formula (I), examples of the C_1-C_6 alkyl group defined by R^1 include methyl group, ethyl group, propyl group, isopropyl group, butyl group, isobutyl group, sec-butyl group, tert-butyl group, pentyl group, isopentyl group, neopentyl group, tert-pentyl group, hexyl group, and isohexyl group. Examples of the C_3-C_7 cycloalkyl group include cyclopropyl group, cyclobutyl group, cyclopentyl group, cyclohexyl group, and cycloheptyl group. Examples of the halogenated C_1-C_4 alkyl group include trifluoromethyl group, trifluoroethyl group, and pentafluoroethyl group. Examples of the halogen atom include fluorine atom, chlorine atom, and bromine atom. Examples of the C_6-C_{12} aryl group include phenyl group and naphthyl group.

Preferred examples of R^1 include a hydrogen atom, a C_1-C_6 alkyl group, a C_5-C_8 cycloalkyl group, trifluoromethyl group, a halogen atom, or a phenyl group, and more preferred examples include C_1-C_3 alkyl group, cyclohexyl group, trifluoromethyl group, a chlorine atom, a bromine atom, or a phenyl group. R^1 is most preferably methyl

group or propyl group.

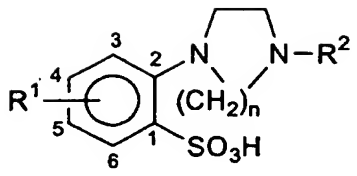
Examples of the C_1-C_6 alkyl group defined by R^2 include, for example, alkyl groups defined as for the aforementioned R^1. Examples of the C_7-C_{12} aralkyl group include, for example, benzyl group, phenethyl group, and naphthylmethyl group. The aralkyl group may have one or more substituents selected from the group consisting of cyano group; nitro group; a C_1-C_6 alkoxyl group such as methoxy group, ethoxy group, propoxy group, isopropoxy group, butoxy group, isobutoxy group, tert-butoxy group, pentyloxy group, isopentyloxy group, tert-pentyloxy group, or hexyloxy group; a halogen atom such as those defined as for the aforementioned R^1; an alkyl group such as those defined as for the aforementioned R^1; and an amino group.

Preferred examples of R^2 include a hydrogen atom, a C_1-C_3 alkyl group, or a C_7-C_{12} aralkyl group which may have one or more substituents selected from the group consisting of a C_1-C_3 alkyl group, a C_1-C_3 alkoxyl group, and a halogen atom, and more preferred examples include a hydrogen atom or a C_7-C_{12} aralkyl group which may have one or more substituents selected from the group consisting of a C_1-C_3 alkoxyl group. R^2 is most preferably a hydrogen atom.

In the aforementioned general formula (I), symbol n is preferably 2.

Specific examples of the compounds represented by the aforementioned general formula (I), which are preferred as active ingredients of the medicament of the present invention, include the compounds listed in the following tables 1 and 2.

Table 1



Compound No.	Substituting position of R^1	R^1	n	R^2
1	–	H	2	H
2	3	$-CH_3$	2	H
3	3	$-CH_2CH_3$	2	H
4	3	$-CH_2CH_2CH_3$	2	H
5	3	$-CH(CH_3)_2$	2	H
6	3	$-(CH_2)_3CH_3$	2	H
7	4	$-CH_3$	2	H
8	4	$-CH_2CH_3$	2	H
9	4	$-(CH_2)_2CH_3$	2	H
10	4	$-CH(CH_3)_2$	2	H
11	4	$-(CH_2)_3CH_3$	2	H
12	5	$-CH_3$	2	H
13	5	$-CH_2CH_3$	2	H
14	5	$-(CH_2)_2CH_3$	2	H
15	5	$-CH(CH_3)_2$	2	H

Table 1 (continued)

Compound No.	Substituting position of R^1	R^1	n	R^2
16	5	$-(CH_2)_3CH_3$	2	H
17	5	$-(CH_2)_4CH_3$	2	H
18	5	$-(CH_2)_5CH_3$	2	H
19	6	$-CH_3$	2	H
20	6	$-CH_2CH_3$	2	H
21	6	$-(CH_2)_2CH_3$	2	H
22	-	H	2	$-CH_3$
23	3	$-CH_2CH_3$	2	$-CH_3$
24	3	$-(CH_2)_2CH_3$	2	$-CH_3$
25	3	$-CH(CH_3)_2$	2	$-CH_3$
26	3	$-(CH_2)_3CH_3$	2	$-CH_3$
27	4	$-CH_3$	2	$-CH_3$
28	4	$-CH_2CH_3$	2	$-CH_3$
29	4	$-(CH_2)_2CH_3$	2	$-CH_3$
30	5	$-CH_3$	2	$-CH_3$
31	5	$-CH_2CH_3$	2	$-CH_3$

Table 1 (continued)

Compound No.	Substituting position of R^1	R^1	n	R^2
32	5	$-(CH_2)_2CH_3$	2	$-CH_3$
33	5	$-CH(CH_3)_2$	2	$-CH_3$
34	5	$-(CH_2)_3CH_3$	2	$-CH_3$
35	5	$-(CH_2)_4CH_3$	2	$-CH_3$
36	5	$-(CH_2)_5CH_3$	2	$-CH_3$
37	6	$-CH_3$	2	$-CH_3$
38	6	$-CH_2CH_3$	2	$-CH_3$
39	6	$-(CH_2)_2CH_3$	2	$-CH_3$
40	6	$-CH(CH_3)_2$	2	$-CH_3$
41	6	$-(CH_2)_3CH_3$	2	$-CH_3$
42	3	$-(CH_2)_2CH_3$	2	$-(CH_2)_2CH_3$
43	4	$-(CH_2)_2CH_3$	2	$-(CH_2)_2CH_3$
44	5	$-CH_3$	2	$-(CH_2)_2CH_3$
45	5	$-CH_2CH_3$	2	$-(CH_2)_2CH_3$
46	5	$-(CH_2)_2CH_3$	2	$-(CH_2)_2CH_3$
47	5	$-CH(CH_3)_2$	2	$-(CH_2)_2CH_3$

Table 1 (continued)

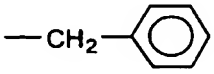
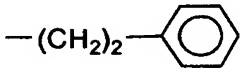
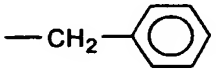
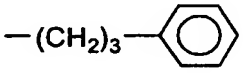
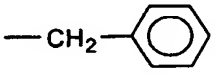
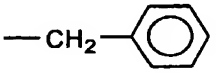
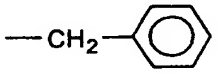
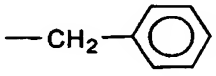
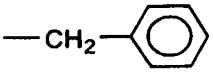
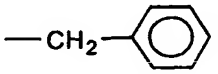
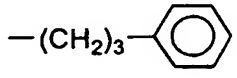
Compound No.	Substituting position of R^1	R^1	n	R^2
48	5	$-(CH_2)_3CH_3$	2	$-(CH_2)_2CH_3$
49	5	$-(CH_2)_5CH_3$	2	$-(CH_2)_2CH_3$
50	-	H	2	$-(CH_2)_2CH_3$
51	-	H	2	
52	3	$-CH_3$	2	
53	3	$-(CH_2)_2CH_3$	2	
54	4	$-CH_3$	2	
55	4	$-(CH_2)_2CH_3$	2	
56	5	$-CH_3$	2	
57	5	$-CH_2CH_3$	2	
58	5	$-(CH_2)_2CH_3$	2	
59	5	$-CH(CH_3)_2$	2	
60	5	$-(CH_2)_3CH_3$	2	
61	5	$-(CH_2)_4CH_3$	2	

Table 1 (continued)

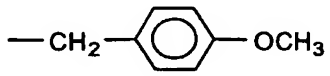
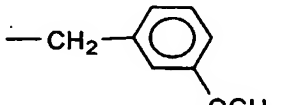
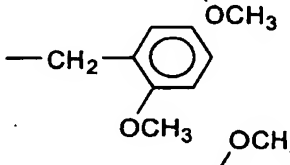
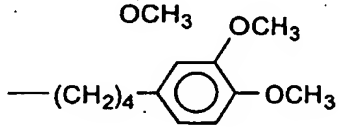
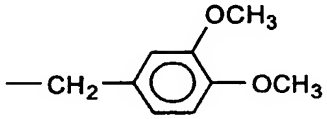
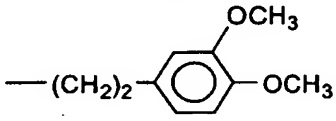
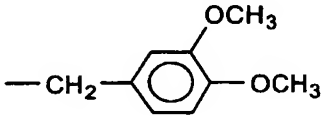
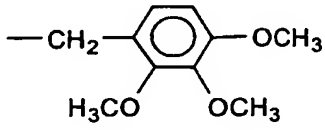
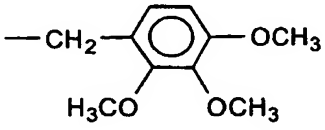
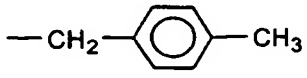
Compound No.	Substituting position of R^1	R^1	n	R^2
62	5	$-(CH_2)_2CH_3$	2	
63	5	$-CH(CH_3)_2$	2	
64	5	$-CH(CH_3)_2$	2	
65	4	$-(CH_2)_2CH_3$	2	
66	5	$-(CH_2)_2CH_3$	2	
67	5	$-CH(CH_3)_2$	2	
68	6	$-(CH_2)_2CH_3$	2	
69	5	$-(CH_2)_2CH_3$	2	
70	6	$-(CH_2)_2CH_3$	2	
71	3	$-(CH_2)_2CH_3$	2	

Table 1 (continued)

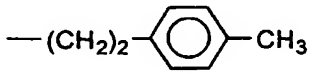
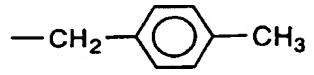
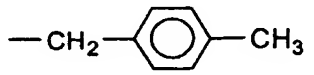
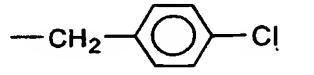
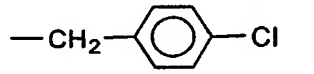
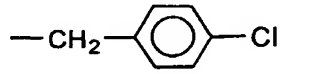
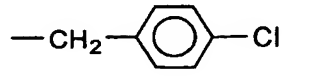
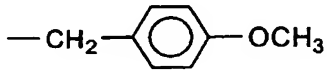
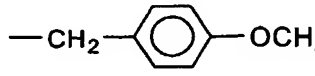
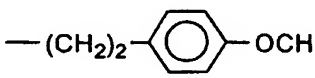
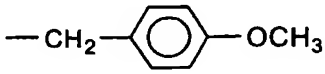
Compound No.	Substituting position of R^1	R^1	n	R^2
72	4	$-(CH_2)_2CH_3$	2	
73	5	$-(CH_2)_2CH_3$	2	
74	6	$-CH(CH_3)_2$	2	
75	3	$-(CH_2)_2CH_3$	2	
76	4	$-(CH_2)_2CH_3$	2	
77	5	$-(CH_2)_2CH_3$	2	
78	6	$-(CH_2)_2CH_3$	2	
79	3	$-(CH_2)_2CH_3$	2	
80	4	$-(CH_2)_2CH_3$	2	
81	5	$-(CH_2)_2CH_3$	2	
82	6	$-(CH_2)_2CH_3$	2	
83	-	H	3	H
84	5	$-CH_3$	3	H

Table 1 (continued)

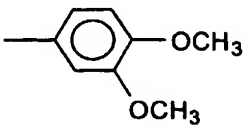
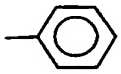
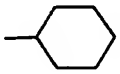
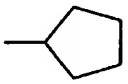
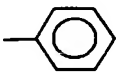
Compound No.	Substituting position of R^1	R^1	n	R^2
85	5	$-CH_2CH_3$	3	H
86	5	$-(CH_2)_2CH_3$	3	H
87	5	$-CH(CH_3)_2$	3	H
88	5	$-(CH_2)_2CH_3$	3	H
89	5	$-(CH_2)_2CH_3$	3	$-CH_3$
90	5	$-(CH_2)_2CH_3$	3	
91	5		2	H
92	5	$-F$	2	H
93	5	$-Cl$	2	H
94	5	$-Br$	2	H
95	5	$-CF_3$	2	H
96	5		2	H
97	5		2	H
98	5		2	$-CH_3$
99	5	$-Cl$	2	$-CH_3$

Table 1 (continued)

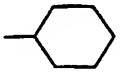
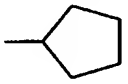
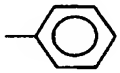
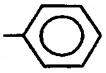
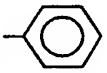
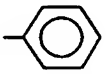
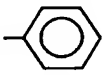
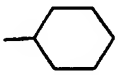
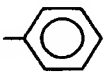
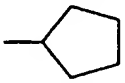
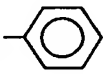
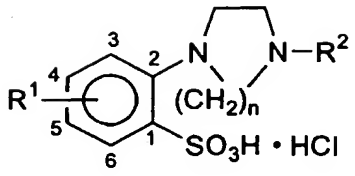
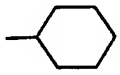
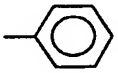
Compound No.	Substituting position of R^1	R^1	n	R^2
100	5	—Br	2	$-CH_3$
101	5	$-CF_3$	2	$-CH_3$
102	5		2	$-CH_3$
103	5		2	$-CH_3$
104	5		2	$-CH_2$ 
105	5	—Cl	2	$-CH_2$ 
106	5	—Br	2	$-CH_2$ 
107	5	$-CF_3$	2	$-CH_2$ 
108	5		2	$-CH_2$ 
109	5		2	$-CH_2$ 

Table 2



Compound No.	Substituting position of R^1	R^1	n	R^2
110	5	$-CH_2CH_2CH_3$	2	H
111	5	$-CH(CH_3)_2$	2	H
112	5		2	H
113	5		2	H
114	5	—Cl	2	H
115	5	—Br	2	H
116	5	$-CF_3$	2	H

In the tables 1 and 2, the compounds wherein the substituting position is position-5 are preferred, and more preferred compounds include the following compounds:

5-methyl-2-(1-piperazinyl)benzenesulfonic acid;

5-trifluoromethyl-2-(1-piperazinyl)benzenesulfonic acid;

5-n-propyl-2-(1-piperazinyl)benzenesulfonic acid;

5-phenyl-2-(1-piperazinyl)benzenesulfonic acid;

5-chloro-2-(1-piperazinyl)benzenesulfonic acid;

5-bromo-2-(1-piperazinyl)benzenesulfonic acid;

5-isopropyl-2-(1-piperazinyl)benzenesulfonic acid;

5-cyclohexyl-2-(1-piperazinyl)benzenesulfonic acid;

5-n-propyl-2-(1-homopiperazinyl)benzenesulfonic acid;

5-n-propyl-2-[4-(2,3,4-trimethoxybenzyl)-1-piperazinyl]benzenesulfonic acid; and

5-n-propyl-2-[4-(3,4-dimethoxybenzyl)-1-piperazinyl]benzenesulfonic acid.

Among the aforementioned compounds, most preferable examples include 5-methyl-2-(1-piperazinyl)benzenesulfonic acid and 5-n-propyl-2-(1-piperazinyl)-benzenesulfonic acid.

Pharmaceutically acceptable salts of the aforementioned compounds can also be used as active ingredients of the medicament of the present invention. Examples of salts of the aforementioned compounds include, for example, alkali metal salts and alkaline earth metal salts such as sodium salts, potassium salts, magnesium salts, calcium salts, or aluminum salts; ammonium salts; amine salts such as lower alkylamine salts such as triethylamine salts, hydroxy-lower alkylamine salts such as 2-hydroxyethylamine salts, bis-(2-hydroxyethyl)amine salts, tris(hydroxymethyl)aminomethane salts, or N-methyl-D-glucamine salts, cycloalkylamine salts such as dicyclohexylamine salts, benzylamine salts such as N,N-dibenzylethylenediamine salts or dibenzylamine salts; inorganic acid salts such as hydrochloric acid salts, hydrobromic acid salts, sulfuric acid salts, or phosphoric acid salts; and organic acid salts such as, for example, fumaric acid salts, succinic acid salts, oxalic acid salts, or lactic acid salts.

In addition to the compounds in free form or salts, any hydrates or solvates thereof can also be used as an active ingredient of the medicament of the present invention. Examples of solvents which can form the solvates of the aforementioned compound include, for example, methanol, ethanol, isopropyl alcohol, acetone, ethyl acetate, methylene chloride and the like.

A most preferred example of the active ingredient of the medicament of the

present invention includes 5-methyl-2-(1-piperazinyl)benzenesulfonic acid monohydrate.

The aminobenzenesulfonic acid derivatives represented by the aforementioned general formula (I) are known. For example, according to the methods described in Japanese Patent Unexamined Publication (KOKAI) Nos. 3-7263 and 9-221479, European Patent Publication Nos. 390654 and 779283, and U.S. Patent Nos. 5053409 and 5990113 and the like, one or ordinary skill in the art can readily synthesize and obtain said compounds.

As the medicament of the present invention, a substance, per se, which is selected from the group consisting of the aminobenzenesulfonic acid derivative represented by the above general formula (I) and a salt thereof, and a hydrate thereof and a solvate thereof can be administered. Alternatively, a pharmaceutical composition comprising the aforementioned substance as an active ingredient and one or more pharmaceutical additive can be prepared and administered.

The medicament of the present invention can be orally or parenterally administered to a mammal including a human. Examples of the forms of pharmaceutical compositions suitable for oral administration include granules, subtilized granules, powders, tablets, hard capsules, soft capsules, syrups, emulsions, suspensions, solutions and the like. Examples of the forms of pharmaceutical compositions suitable for parenteral administration include injections, a suppositories, transdermal preparations and the like.

For manufacture of the aforementioned pharmaceutical compositions, such as a solid or liquid pharmaceutical carriers, or ordinarily used pharmaceutical additives such as excipients, stabilizers, lubricants, sweetening agents, preservatives, suspending aids and the like can be used. A ratio of the active ingredient to the pharmaceutical additive is not particularly limited. For example, the ratio may preferably be 1 to 90% by weight.

Examples of solid pharmaceutical additives include, for example, lactose, kaolin, sucrose, crystalline cellulose, cornstarch, talc, agar, pectin, acacia, stearic acid, magnesium stearate, lecithin, sodium chloride and the like. Examples of liquid carriers include syrup, glycerol, peanut oil, polyvinylpyrrolidone, olive oil, ethanol, benzyl alcohol, propylene glycol, water and the like.

A dose of the medicament of the present invention can be suitably determined depending on, for example, a purpose of treatment or prevention, a kind of a disorder to be treated or prevented, symptoms, body weight, age, and sexuality of a patient, and a kind of the aforementioned substance as an active ingredient. For example, a dose of 0.01 to 1,000mg per day as the weight of the compound represented by the aforementioned general formula (I) can generally be administered orally to an adult. The above dose may preferably be administered once a day or several times a day as divided portions.

Example

The present invention will be more specifically explained by an example. However, the scope of the present invention is not limited to the example.

In the following example, 5-methyl-2-(1-piperazinyl)benzenesulfonic acid monohydrate was used as the active ingredient of the medicament of the present invention (hereinafter referred to as "the medicament of the present invention"). This substance was prepared according to Example 1 of Japanese Patent Unexamined Publication (KOKAI) No. 9-221479.

(Experimental Methods)

The heart of the rat was excised and perfused with Krebs buffer solution (in mM: NaCl 119, KCl 4.6, $MgSO_4 \cdot 7H_2O$ 1.2, $CaCl_2 \cdot 2H_2O$ 1.3, $NaHCO_3$ 25, KH_2PO_4 1.2, glucose 11; pH 7.4, 37°C) according to Langendorff method. A thread attached to the apex of the heart was connected to a tension transducer to determine contractile

tension. The heart was perfused with a perfusion solution containing monensin (5 μM; sodium ionophore) for 10 min and then ischemia was induced by a cessation of coronary flow (for 15 min). After reperfusion for 30 min, the heart was liquefied in nitric acid, and ventricular total calcium content was determined by atomic absorption analysis. Contractile tension was measured during the experiment, and recovery in contractile tension at 30 min of reperfusion related to its pre-value was used as an index of cardiac contraction.

(Results)

The results are shown in Table 3. In the table, ** represents $p<0.01$ vs. control by Dunnett's multiple comparison test, and *** represents $P<0.001$ vs. control by Dunnett's multiple comparison test.

In the heart treated with ischemia/reperfusion in combination with monensin treatment (control), increase in ventricular total calcium content and decrease in recovery in contractile tension were observed compared with those in normoxic hearts (normal). Since the increase in calcium content was dependent on intracellular sodium, the Ca^{++} influx was considered to be mediated by sodium/calcium exchanger. Further, the decrease in recovery in contractile tension was small in the absence of moneisin, suggesting that the decrease was related to the increase in calcium content. The medicament of the present invention improved the increased ventricular calcium content and the decreased recovery in contractile tension which were induced by moneisin treatment and ischemia/reperfusion. Diltiazem (a calcium antagonist; purchased from Sigma) and Amiloride (an inhibitor of sodium/proton exchanger; purchased from Sigma) failed to exhibit these effects.

Table 3. The effect of the medicament of the present invention on ventricular calcium content and recovery in contractile tension

Group	N	Calcium Content (μ mol/g)	Recovery in Contractile Tension (%)
Normal	8	2.15±0.11**	91.2±2.9***
Without Moneisin	8	2.19±0.13	65.0±5.3
Control	8	6.20±0.23	5.3±2.1
Compound of the Present Invention 10^{-7} M	8	3.72±0.16**	24.9±4.4**
Compound of the Present Invention 10^{-6} M	8	2.72±0.18**	38.5±7.5***
Diltiazem 10^{-6} M	8	5.75±0.16	11.0±3.3
Diltiazem 10^{-5} M	8	5.89±0.22	7.4±2.0
Amiloride 10^{-4} M	8	5.30±0.25	8.9±2.2
Amiloride 10^{-3} M	8	4.26±0.40	15.6±2.9

From the above results, the medicament of the present invention was demonstrated to be effective in reducing increase in ventricular calcium content induced by sodium overload and ischemia/reperfusion based on inhibition of the sodium/calcium exchanger.

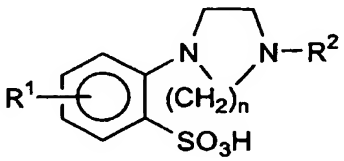
Industrial Applicability

A novel class of medicament inhibiting sodium/calcium exchange system is provided by the present invention. The medicament of the present invention is effective for suppression of intracellular calcium accumulation generated

under very severe dyscrasic condition as a result of clinically-occurred combination of ischemia/reperfusion and intracellular sodium increase.

CLAIMS

1. A medicament for inhibiting sodium/calcium exchange system which comprises as an active ingredient a substance selected from the group consisting of an aminobenzenesulfonic acid derivative represented by the following general formula (I) and a salt thereof, and a hydrate thereof and a solvate thereof:



··· (I)

wherein R^1 represents a hydrogen atom, a C_1-C_6 alkyl group, a C_3-C_7 cycloalkyl group, a halogenated C_1-C_4 alkyl group, a halogen atom, or a C_6-C_{12} aryl group; R^2 represents a hydrogen atom, a C_1-C_6 alkyl group, or a C_7-C_{12} aralkyl group which may have one or more substituents selected from the group consisting of cyano group, nitro group, a C_1-C_6 alkoxyl group, a halogen atom, a C_1-C_6 alkyl group, and amino group; and n represents an integer of from 1 to 4.

2. The medicament according to claim 1, which is used for therapeutic and/or preventive treatment of a dysfunction resulting from ischemia/reperfusion.

3. The medicament according to claims 1 or 2, which is used for suppressing increase in myocardium calcium content induced by a dysfunction resulting from ischemia/reperfusion.

4. The medicament according to any one of claims 1 to 3, which is used for suppressing increase of myocardium calcium content generated under condition of a combination of ischemia/reperfusion and increase of myocardium sodium content.

5. The medicament according to any one of claims 1 to 4, wherein substituting position of R^1 is position-5.

6. The medicament according to any one of claims 1 to 5, wherein n is 2.

7. The medicament according to any one of claims 1 to 6, wherein R^2 is a hydrogen atom, a C_1-C_3 alkyl group, or a C_7-C_{12} aralkyl group which may have one or more substituents selected from the group consisting of a C_1-C_3 alkyl group, a C_1-C_3 alkoxyl group, and a halogen atom.

8. The medicament according to any one of claims 1 to 7, wherein R^2 is a hydrogen atom or a C_7-C_{12} aralkyl group which may have one or more substituents selected from the group consisting of a C_1-C_3 alkoxyl group.

9. The medicament according to any one of claims 1 to 8, wherein R^2 is a hydrogen atom.

10. The medicament according to any one of claims 1 to 9, wherein R^1 is a hydrogen atom, a C_1-C_6 alkyl group, a C_5-C_6 cycloalkyl group, trifluoromethyl group, a halogen atom, or a phenyl group.

11. The medicament according to any one of claims 1 to 10, wherein R^1 is a C_1-C_3 alkyl group, cyclohexyl group, trifluoromethyl group, a chlorine atom, a bromine atom, or phenyl group.

12. The medicament according to any one of claims 1 to 11, wherein R^1 is methyl group or propyl group.

13. The medicament according to any one of claims 1 to 4, wherein the active ingredient is a substance selected from the group consisting of the following compounds:

5-methyl-2-(1-piperazinyl)benzenesulfonic acid;

5-trifluoromethyl-2-(1-piperazinyl)benzenesulfonic acid;

5-n-propyl-2-(1-piperazinyl)benzenesulfonic acid;

5-phenyl-2-(1-piperazinyl)benzenesulfonic acid;

5-chloro-2-(1-piperazinyl)benzenesulfonic acid;

5-bromo-2-(1-piperazinyl)benzenesulfonic acid;

5-isopropyl-2-(1-piperazinyl)benzenesulfonic acid;

5-cyclohexyl-2-(1-piperazinyl)benzenesulfonic acid;

5-n-propyl-2-(1-homopiperazinyl)benzenesulfonic acid;

5-n-propyl-2-[4-(2,3,4-trimethoxybenzyl)-1-piperazinyl]benzenesulfonic acid; and

5-n-propyl-2-[4-(3,4-dimethoxybenzyl)-1-piperazinyl]benzenesulfonic acid

and a salt thereof, and a hydrate thereof and a solvate thereof.

14. The medicament according to claim 13, wherein the active ingredient is a substance selected from the group consisting of the following compounds:

5-methyl-2-(1-piperazinyl)benzenesulfonic acid and

5-n-propyl-2-(1-piperazinyl)benzenesulfonic acid

and a salt thereof, and a hydrate thereof and a solvate thereof.

15. The medicament according to any one of claims 1 to 14, wherein the active ingredient is 5-methyl-2-(1-piperazinyl)benzenesulfonic acid monohydrate.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/JP 02/07486

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61P9/10 A61K31/395 A61K31/4164 A61K31/495 A61K31/551

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
CHEM ABS Data, SCISEARCH, EMBASE, MEDLINE, BIOSIS, EPO-Internal, WPI Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 390 654 A (MITSUBISHI CHEM IND) 3 October 1990 (1990-10-03) cited in the application page 2, line 1 - line 43 table 1 page 15 -page 17; examples 1,2 claims 1-21	1-15
X	US 6 245 767 B1 (NAGANO TATSUO ET AL) 12 June 2001 (2001-06-12) column 4, line 66 -column 6, line 2 claims 1,4-19	1-15

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
17 October 2002	31/10/2002

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	van der Kooij, M

2

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/JP 02/07486

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	PATENT ABSTRACTS OF JAPAN vol. 1997, no. 12, 25 December 1997 (1997-12-25) & JP 09 221479 A (MITSUBISHI CHEM CORP), 26 August 1997 (1997-08-26) cited in the application abstract	1-15
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Y	DATABASE WPI Section Ch, Week 200153 Derwent Publications Ltd., London, GB; Class B03, AN 2001-488606 XP002216400 & WO 01 45739 A (MITSUBISHI-TOKYO PHARM INC), 28 June 2001 (2001-06-28) abstract	1-15

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2

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/JP 02/07486

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
Y	HASHIMOTO KEITARO ET AL: "A Na+/Ca2+ exchange inhibitor, KB-R7943, on digitalis and ischemia-reperfusion arrhythmia models." JOURNAL OF MOLECULAR AND CELLULAR CARDIOLOGY, vol. 33, no. 6, June 2001 (2001-06), page A45 XP008009275 XVII ISHR World Congress of the International Society for Heart Research;Winnipeg, Canada; July 06-11, 2001 ISSN: 0022-2828 abstract	1-15
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Y	OKUMURA HIROYUKI ET AL: "Na+/Ca2+ exchanger and protective effect of ischemic preconditioning in perfused rat hearts." JIKEIKAI MEDICAL JOURNAL, vol. 47, no. 4, December 2000 (2000-12), pages 153-166, XP008009274 ISSN: 0021-6968 abstract page 164, paragraph 3	1-15
A	MATSUDA TOSHIO ET AL: "SEA0400, a novel and selective inhibitor of the Na+-Ca2+ exchanger, attenuates reperfusion injury in the in vitro and in vivo cerebral ischemic models." JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS, vol. 298, no. 1, July 2001 (2001-07), pages 249-256, XP008009273 ISSN: 0022-3565 abstract page 255, column 1, paragraph 2 -column 2, paragraph 2	1-15

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2

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/JP 02/07486

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	TAKAHASHI TEISUKE ET AL: "Na+/Ca2+ exchange may play an important role in ischemia-reperfusion injury in in vivo heart and brain." JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY, vol. 37, no. 2 Supplement A, February 2001 (2001-02), page 324A XP008009281 50th Annual Scientific Session of the American College of Cardiology;Orlando, Florida, USA; March 18-21, 2001 ISSN: 0735-1097 abstract	1-15

2

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP 02/07486

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Present claims 1 and 3-15 relate to the treatment of a disease which actually is not well defined.
The use of the definitions "inhibiting sodium/calcium exchange system" (claims 1 and 5-15), "suppressing increase in myocardium calcium content" (claim 3, 4 and 5-15) in the present context is considered to lead to a lack of clarity within the meaning of Article 6 PCT. It is not fully possible to determine the diseases for which protection might legitimately be sought. The lack of clarity is such as to render a meaningful complete search impossible. Consequently, the search has been restricted to the real and defined disease state mentioned in claim 2, namely ischemia/reperfusion with due regard to the general idea underlying the present invention.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

Information on patent family members

International Application No
PCT/JP 02/07486

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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